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CLAIMS

1. Microcapsules or microballoons of micronic or sub-micronic size bounded by a polymer membrane filled with air or a gas suitable, when in the form of suspensions in a liquid carrier, to be administered to human or animal patients for therapeutic or diagnostic applications, e.g. for the purpose of ultrasonic echography imaging, characterized in that the polymer of the membrane is a deformable and resilient interfacially deposited polymer.

2. Air or gas filled microballoons bounded by an elastic interfacial polymeric membrane adapted to form with suitable physiologically acceptable aqueous carrier liquids suspensions to be taken orally, rectally and urethrally, or injectable into living organisms for therapeutic or diagnostic purposes, characterized in being non-coalescent dry and instantly dispersible by admixing with said liquid carrier.

3. The microballoons of claims 1 or 2 having size mostly in the 0.5 - 10 μm range suitable for injection into the blood-stream of living beings, characterized in that the membrane polymer is biodegradable and the membrane is either impervious or contains pores permeable to bioactive liquids for increasing the rate of biodegradation.

4. The microballoons of claim 3, in which the polymer membrane has a porosity ranging from a few nanometers to several hundreds or thousands of nanometers, preferably 50-2000 nm.

5. The microballoons of claim 3, in which the membrane is lastic, has a thickness of 50-500 nm, and resists pressure variations produced by heart beat pulsations in the blood-stream.

6. The microballoons of claim 3, in which the polymer of the membrane is a biodegradable polymer selected from poly-saccharides, polyamino-acids, polylactides and polyglycolides and their copolymers, copolymers of lactides and lactones, polypeptides, poly-(ortho)esters, polydioxanone, poly-β-amino-ketones, polyphosphazenes, polyanhydrides and poly(alkyl-cyano-acrylates).

7. The microballoons of claim 3, in which the membrane

polymer is selected from polyglutamic or polyaspartic acid derivatives and their copolymers with other amino-acids.

8. The microballoons of claim 7, in which the polyglutamic and polyaspartic acid derivatives are selected from esters and amides involving the carboxylated side function thereof, said side functions having formulae

$$-(CH_2)_nCOO-CHR^1COOR \qquad (I), \quad \text{or}$$

$$-(CH_2)_nCOOR^1R^2-O-COR \qquad (II), \quad \text{or}$$

$$-(CH_2)_nCO(NH-CHX-CO)_mNHCH(COOH)-(CH_2)_pCOOH \qquad (III),$$

in which R is an alkyl or aryl substituent; R^1 and R^2 are H or lower alkyls, or R and R^1 are connected together by a substituted or unsubstituted linking member to form a 5- or 6-membered ring; n is 1 or 2; p is 1, 2 or 3; m is an integer from 1 to 5 and X is a side chain of an aminoacid residue.

9. The microballoons of claim 3, in which the membrane polymer contains additives to control the degree of elasticity, and the size and density of the pores for permeability control.

10. The microballoons of claim 9, in which said additives include plasticizers, amphipatic substances and hydrophobic compounds.

11. The microballoons of claim 10, in which the plasticizers include isopropyl myristate, glyceryl monostearate and the like to control flexibility, the amphipatic substances include surfactants and phospholipids like the lecithins to control permeability by increasing porosity and the hydrophobic compounds include high molecular weight hydrocarbon like the paraffin-waxes to reduce porosity.

12. The microballoons of claim 10, in which the additives include polymers of low molecular weight, e.g. in the range of 1000 to 15.000, to control softness and resiliency of th microballoon membrane.

13. The microballoons of claim 12, in which the low molecular weight polymer additiv s ar select d from polylacti-

des, polyglycolides, polyalkylene glycols like polyethylene glycol and polypropylene glycol, and polyols like polyglycerol.

14. The microballoons of claims 1 or 2, having size up to about 1000 µm suitable for oral, rectal and urethral applications, characterized in that the membrane polymer is not biodegradable in the digestive tract and impervious to biological liquids.

15. The microballoons of claim 14, in which the polymer is selected from polyolefins, polyacrylates, polyacrylonitrile, non-hydrolyzable polyesters, polyurethanes and polyureas.

16. Aqueous suspension of the microballoons according to claims 1 or 2 for administration to patients, characterized in containing a concentration of about 10^6 to 10^{10} microballoons/ml, this being stable for a period exceeding a month.

17. A method for making air or gas filled microballoons usable as suspensions in a carrier liquid for oral, rectal and urethral applications, or for injections into living organisms, this method comprising the steps of:

(1) emulsifying a hydrophobic organic phase into a water phase so as to obtain droplets of said hydrophobic phase as an oil-in-water emulsion in said water phase;

(2) adding to said emulsion a solution of at least one polymer in a volatile solvent insoluble in the water phase, so that a layer of said polymer will form around said droplets;

(3) evaporating said volatile solvent so that the polymer will deposit by interfacial precipitation around the droplets which then form beads with a core of said hydrophobic phase ncapsulated by a membrane of said polymer, said beads being in suspension in said water phase;

(4) subjecting said suspension to reduced pressure under conditions such that said encapsulated hydrophobic phase be removed by evaporation;

characterized in that said hydrophobic phase is selected so that in st p (4) it vaporates substantially simultan ously with the water phase and is replaced by air or gas, wh reby dry, free flowing, readily dispersible microballoons are obtained.

18. The method of claim 17, in which said polymer is

dissolved in said hydrophobic phase, so that steps (2) and (3) can be omitted and the polymer membrane will form by interfacial precipitation during step (4).

19. The method of claim 17, characterized in that evaporation of said hydrophobic phase in step (4) is performed at a temperature where the partial vapour pressure of said hydrophobic phase is of the same order as that of water vapour.

20. The method of claim 17, in which said evaporation of step (4) is carried out under freeze-drying conditions.

21. The method of claim 17, in which freeze-drying is ffected at temperatures of from -40°C to 0°C.

22. The method of claims 17 or 9, in which the hydrophobic phase is selected from organic compounds having a vapour pressure of about 1 Torr at a temperature comprised in the interval of about -40°C to 0°C.

23. The method of claims 17 or 18, in which the aqueous phase comprises, dissolved, from about 1 to 20% by weight of stabilizers comprising hydrophilic compound selected from sugars, PVA, PVP, gelatin, starch, dextran, polydextrose, albumin and the like.

24. The method of claim 18, in which additives to control the degree of permeability of the microballoons membrane are added to the hydrophobic phase, the rate of biodegradability of the polymer after injecting the microballoons into living organisms being a function of said degree of permeability.

25. The method of claim 24, in which the said additives include hydrophobic solids like fats, waxes and high molecular w ight hydrocarbons, the presence of which in the membrane polymer of the microballoons will reduce permeability toward aqueous liquids.

26. The method of claim 24, in which the said additives include amphipatic compounds like the phospholipids, or low molecular weight polymers, the presence of which in the membrane polymer will increase permeability of the microballoons to aqueous liquids.

27. The m thod of claim 18, in which the hydrophobic phase subjected to mulsification in said wat r phase also contains a

water-soluble solvent which, upon being diluted into said water phase during emulsification, will aid in reducing the size of droplets and induce interfacial precipitation of the polymer before step (4) is carried out.

28. A method for making air or gas filled microballoons usable as suspensions in a carrier liquid for oral, rectal and urethral applications, or for injections into living organisms, this method comprising the steps of:

(1) emulsifying a hydrophobic organic phase into a water phase so as to obtain droplets of said hydrophobic organic phase as an oil-in-water emulsion in said water phase, said organic phase containing, dissolved therein, one or more water-insoluble polymers;

(2) subjecting said emulsion to reduced pressure under conditions such that said hydrophobic phase be removed by evaporation, whereby the polymer dissolved in the droplets will deposit interfacially and form a polymer bounding membrane, the droplets being simultaneously converted to microballoons,

characterized in that said hydrophobic phase is selected so that in step (2) it evaporates substantially simultaneously with the water phase and, upon evaporation, is replaced by air or gas, whereby the microballoons obtained are in dry, free flowing and readily dispersible form.

29. The method of claim 28, in which the hydrophobic polymer solution phase subjected to emulsification in said water phase also contains a water-soluble solvent which, upon being diluted into said water phase during emulsification, will aid in reducing the size of droplets and induce interfacial precipitations of the polymer before step (2) is carried out.

30. The method of claim 28, in which said organic hydrophobic phase emulsified in step (1) contains no polymer dissolved therein, and before carrying through step (2), the following additional steps are perform d:

(1a) adding to said mulsion a solution of at least one polymer in a volatile solvent insoluble in the water phase, so that a layer of said polymer will form around said droplets;

(1b) vaporating said volatile solv nt so that the polymer

will d posit by interfacial precipitation around the droplets, thus forming microballoons or beads with a core of said hydrophobic phase encapsulated by a membrane of said polymer, said beads being in suspension in said water phase, whereby in step (2) evaporation of said hydrophobic phase takes place through said membrane and provides it with substantial micro-porosity.

31. An injectable aqueous suspension of microballoons containing 10^8-10^{10} vesicles/ml bounded by a membrane of interfacially precipitated DL-lactide polymer defined by the commercial name of Resomer.

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